Serum uric acid, serum glucose and diabetes: relationships in a population study

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Summary: The relationships between serum uric acid, serum glucose and diabetes have been examined in a survey of 7735 middle-aged men drawn at random from general practices in 24 British towns. There was a positive relationship between serum glucose and serum uric acid concentrations up to about 8.0 mmol/l; at higher levels of glucose, serum uric acid decreased. Uric acid levels were significantly reduced in insulin-dependent diabetics and in those on oral hypoglycaemics and also in 'non-diabetics' with casual glucose levels > 10 mmol/l.

Both uric acid and glucose concentrations were positively related to body mass index; only uric acid was positively related to alcohol intake. Men on antihypertensive treatment had raised levels of uric acid (significant) and glucose (non-significant). The positive relationship between serum uric acid and serum glucose could not be explained by associations with body mass index, alcohol intake, age, social class, gout or treatment for hypertension. It probably reflects the biochemical interaction between serum glucose and purine metabolism, with increased excretion of uric acid during hyperglycaemia and glycosuria.

Introduction

Interesting relationships have been observed between serum uric acid, serum glucose and diabetes in subjects with gout (Weiss *et al.*, 1957), or diabetes mellitus (Beckett & Lewis, 1960) and in several large population-based studies (Yano *et al.*, 1977; Herman & Goldbourt, 1982). Lower serum uric acid levels have been reported in diabetics (Herman *et al.*, 1967; Yano *et al.*, 1977) and higher levels in prediabetics compared with non-diabetic subjects (Herman *et al.*, 1976). The relationships observed in these and other studies have not been consistent. As there has been no population-based study of the relationships between serum uric acid, serum glucose and diabetes in Great Britain, we have reviewed the findings in the British Regional Heart Study. This is a prospective study of risk factors for ischaemic heart disease in middle aged British men. Given that both serum uric acid and serum glucose are putative risk factors (Klein *et al.*, 1973; Jarrett *et al.*, 1982), their interrelationships require clear definition before examining their role in ischaemic heart disease.

Subjects and methods

In the British Regional Heart Study, 7735 men aged 40–59, randomly selected from the age-sex registers of representative general practices in 24 British towns were examined during January 1978 to June 1980. The criteria used to select the towns and practices, and the methods of data collection have been reported (Shaper *et al.*, 1981). About 420 men per town, aged 40–59 years, were selected at random to produce five-year age groups of equal size. The list of names selected was reviewed by the doctors in the practice, who were asked to exclude those whom they considered would not be able to participate because of severe mental or physical disability. It was emphasized that no attempt should be made to exclude subjects with cardiovascular or other problems, and close scrutiny of the annotated lists reduced the exclusions to approximately 6–10 per practice. The remaining subjects were invited to take part in the study, and 78% attended for examination.

Blood samples were drawn in a *non-fasting* state throughout the day, were stood for 15 minutes and then spun for 10 minutes in evacuated tubes. Separated serum specimens were stored at 4°C and

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delivered to the Wolfson Research Laboratories in Birmingham, the vast majority being analysed by noon on the following day. The biochemical analyses were carried out in a Technicon SMA12/60.

All the men were asked if they had ever been told by a doctor that they had any one of a list of physical illnesses. These included myocardial infarction, diabetes mellitus and gout. They were also asked if they were currently using antihypertensive or antidiabetic drugs. The answers to the questions on diabetes made it possible to subdivide the men into three groups on the basis of whether they reported using insulin, oral hypoglycaemic agents or neither of these. An insulin-dependent group (IDD), an oral hypoglycaemic group and a diet group were identified, the latter comprising all men who said they had diabetes but who were not on insulin or oral hypoglycaemic treatment. The vast majority of men in this study said that they were not diabetic and are referred to in this paper as 'non-diabetic', although some of them are probably diabetic on the basis of their raised casual serum glucose concentrations.

A number of other variables known to be associated with both serum uric acid and glucose concentrations were considered and, where appropriate, were adjusted for: social class, alcohol consumption in eight categories; non-drinkers, special occasion drinkers (once/twice per month), weekend drinkers in three groups (1–2, 3–6 or more than 6 drinks per day), and daily (or most days) drinkers (1–2, 3–6 or more than 6 drinks per day); cigarette smoking (non-smokers, ex-smokers, 1–19, 20, 21–39, 40 or more a day), body mass index (weight/height²) and self-reported diagnoses such as myocardial infarction, gout and drug treatment for hypertension. The adjustments were carried out using multiple regression and no assumptions of functional form were made. Body mass index was split into 10 equal sized groups on the basis of its frequency distribution; it was not assumed that the

relationships between body mass index and uric acid or glucose were linear.

Five men could not be classified by diabetic status and there were missing values for serum uric acid and serum glucose in 54 and 49 men respectively.

In order to display the relationship between glucose and uric acid (Figure 4), the 'non-diabetic' subjects were divided into 16 groups on the basis of their blood glucose concentrations. The groups differ in size, the rationale for this grouping being an interest in the form of the relationship over the whole range of glucose concentration, especially in the tails of the distribution. Equal serum glucose intervals or equal sized groups were not used because of the skew distribution of glucose and the precision to which the measurements were expressed (0.1 mmol/l).

No *P*-values or standard errors are given in Tables I and II. However, approximate standard errors for each mean can be calculated by dividing the standard deviation for all men by $n^{1/2}$ where n is the sample size of the group in question. Because of its skew distribution, geometric means and standard errors are quoted for serum glucose. Thus it is necessary to work with the log (geometric mean) and the log (geometric standard deviation) when calculating confidence limits.

Results

The distribution of the serum glucose concentration in the 7612 'non-diabetic men' (Figure 1) shows distribution with skewing towards the higher levels; 50 men had non-fasting plasma glucose concentrations over 10 mmol/l and are probably undiagnosed diabetics. There were, in addition, 118 known diabetics in the study, of whom 36 were insulin-dependent, 43 took oral hypoglycaemic drugs and 39 were on diet alone (Table I). The severity and the degree of control in these subjects is reflected in the

Table I Mean serum uric acid and (geometric) mean glucose concentrations by diabetic status

<i>Self reported diabetic status</i>	<i>Number</i>	<i>Glucose (μmol/l)</i>	<i>Glucose (% > 10 mmol/l)</i>	<i>Uric acid (μmol/l)</i>	<i>Uric acid adjusted (μmol/l)*</i>
Non-diabetic	7612	5.47	0.7%	359	359
Diabetic					
Diet only	39	6.66	15%	369	357
Oral drugs	43	9.95	53%	307	306
Insulin	36	9.61	53%	286	301
All men, mean (s.d.)	7730	5.51 (1.21†)	1.3%	359 (69)	

*Adjustment is for body mass index and alcohol intake category; †see Methods.

Table II Mean serum uric acid and (geometric) mean glucose concentrations in relation to possible confounding factors

	Number	Glucose (mmol/l)	Uric acid (μ mol/l)
Age (years)			
40–44	1838	5.42	359
45–49	1898	5.50	356
50–54	1974	5.51	361
55–59	2025	5.60	359
Alcohol consumption			
None	466	5.57	345
Occasional	1845	5.48	342
Weekend			
1–2 drinks	725	5.46	346
3–6	1234	5.48	358
> 6	1095	5.53	360
Daily			
1–2 drinks	585	5.50	364
3–6	947	5.49	377
> 6	832	5.60	390
Clinical status			
Gout	197	5.59	424
Anti-hypertensive treatment	375	5.75	413
All men, mean (s.d.)	7735	5.51 (1.21†)	359 (69)

Six men were not classified by alcohol category; †see Methods.

considerably higher mean serum glucose levels in those on insulin or on hypoglycaemic drugs. The proportion of subjects with glucose concentrations above 10 mmol/l is also strikingly different compared with those on diet alone or with the 'non-diabetic' subjects (Table I).

The blood samples were taken throughout the day in a non-fasting condition. Serum glucose exhibited a cyclical pattern with higher levels following the morning and the midday meals and in the late afternoon. Serum uric acid showed no diurnal pattern and therefore any relationships observed between serum glucose and uric acid concentrations could not be due to diurnal variation.

The distribution of serum uric acid concentrations for all men (7681) is normal (Figure 2) and similar to that seen in other population studies (Goldbourt *et al.*, 1980; Zalokar *et al.*, 1972). The mean uric acid concentration for the diabetic subjects on diet treatment is similar to that of the 'non-diabetic' subjects, whereas the insulin-dependent diabetics and those on oral hypoglycaemic drugs have mean concentrations well below these levels (Table I).

Factors which might have an association with serum uric acid or glucose concentration have been examined (Table II). Uric acid concentration is positively associated with alcohol intake, with a 14% increase in those drinking more than 6 drinks daily compared with occasional drinkers. The 375 men currently on anti-hypertensive treatment showed a 15% higher mean uric acid concentration than all men in the study and those with a diagnosis of gout were about 18%

Figure 1 Distribution of casual non-fasting serum glucose concentrations excluding 118 known diabetics.

Figure 2 Distribution of serum uric acid concentration.

higher than all men. All these differences are statistically highly significant. Glucose concentrations increased (non-significantly) with increasing alcohol intake and in men with gout on anti-hypertensive treatment. Neither serum uric acid nor glucose concentration showed any significant or consistent relationship with age, cigarette smoking or social class. Both uric acid and glucose concentrations were strongly associated with the body mass index (Figure 3). Mean uric acid concentration increased by 25% from the lowest to the highest of the ten BMI groupings.

Figure 3 Serum uric acid (●) and serum glucose (■) concentrations by body mass index (weight/height²).

Figure 4 Serum uric acid by serum glucose concentrations (mean $\pm$ s.e.).

Mean glucose increased by 5–6% over this range of body mass index.

The relationship between serum uric acid and glucose concentration in 'non-diabetic' subjects has been examined (Figure 4) and shows a positive association up to about 8.0 mmol/l. Above this level of serum glucose there is no further increase in uric acid concentration and the mean concentration in men with glucose levels greater than 10 mmol/l (334 μ mol/l) is about midway between the levels seen in 'non-diabetic' men or diabetics on diet alone, and the levels in diabetics on insulin or oral hypoglycaemic drugs (Table I). After adjustment for body mass index and alcohol intake the relationship is essentially unaltered except in the 'non-diabetic' subjects with glucose concentrations above 10 mmol/l, in whom the adjusted value for uric acid is markedly reduced, owing to the high mean body mass index in this group.

Discussion

The finding of a positive relationship between serum glucose and serum uric acid concentrations up to about 8 mmol/l glucose and a decrease in serum uric acid thereafter is in keeping with the observations made in a large prospective study in Israel (Herman & Goldbourt, 1982). In that study it was shown that prediabetic subjects (non-diabetic at one survey but diabetic at a subsequent survey) had higher uric acid levels than non-diabetics, and that overt (clinically diagnosed) diabetics had lower uric acid levels than non-diabetics. Their finding of a negative association at the highest extreme of the glucose distribution is supported by the negative association between serum

glucose and uric acid concentrations seen in all the diabetic groups in the present study. Further, the 50 'non-diabetics' with glucose concentrations greater than 10 mmol/l had a mean uric acid level significantly lower ($P < 0.01$) than other 'non-diabetics', although not as low as the oral hypoglycaemic or insulin groups. This suggests that the negative relationship is due to the hyperglycaemia and not the treatment provided for the diabetic condition. In healthy volunteers it has been observed that uric acid excretion is directly proportional to serum glucose levels, provided that the glucose load is sufficient to cause glycosuria (Boner & Rieselback, 1974; Herman & Keynan, 1969). No change in uric acid excretion was seen unless glycosuria was present. The finding of low levels of uric acid in diabetes could then be explained by the intermittent or constant hyperglycaemia and glycosuria experienced by diabetic subjects. A cross-sectional study such as ours cannot provide a definitive answer; further experimental studies are indicated.

Glycosuria usually occurs when the blood glucose concentration is greater than 10 mmol/l, though this threshold varies considerably between individuals and increases with age (Butterfield *et al.*, 1967). Given the distribution of serum glucose concentration in the insulin-dependent and oral hypoglycaemic diabetic and in the 50 'non-diabetics' with serum glucoses above 10 mmol/l in this study, it seems likely that, despite treatment, many of these men were spending at least a part of each day in a hyperglycaemic and glycosuric state.

Because treatment with thiazide diuretics in hypertensive subjects may induce both hyperuricaemia and hyperglycaemia (Dollery *et al.*, 1962) analyses of the data in this study have been repeated after excluding all hypertensive subjects on treatment. Although men on hypertensive therapy had higher glucose and uric acid levels than those not on treatment, their exclusion did not affect the findings, nor did exclusion of

patients who recalled a diagnosis of gout.

It has been suggested that increased serum uric acid is a function of decreased renal function. In the present study we found a positive association between serum creatinine and uric acid ($r = 0.25$), but the relationship between serum glucose and uric acid was not altered when the association between creatinine and uric acid was taken into account. The positive association between serum glucose and uric acid concentrations up to the level of about 8 mmol/l serum glucose is not dependent upon the associated effects of body mass index, alcohol intake, gout or treatment for hypertension. The relationship probably reflects the interaction between glucose and purine metabolism via the phosphorylation of glucose to glucose-6-phosphate (Herman & Goldbourt, 1982).

Conclusion

This paper presents the pattern of relationships between serum uric acid, serum glucose and diabetes mellitus for a population of middle-aged British men. It confirms and extends the findings of other population-based studies and draws attention to a relationship which must be considered when examining the role of serum uric acid and serum glucose, diabetes and gout, in the development of ischaemic heart disease.

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